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Allowing for informative missingness in aggregate data meta-analysis with continuous or binary outcomes: Extensions to metamiss

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Abstract. Missing outcome data can invalidate the results of randomized trials and their meta-analysis. However, addressing missing data is often a challenging issue because it requires untestable assumptions. The impact of missing outcome data on the meta-analysis summary effect can be explored by assuming a relationship between the outcome in the observed and the missing participants via an informative missingness parameter. The informative missingness parameters cannot be estimated from the observed data, but they can be specified, with associated uncertainty, using evidence external to the meta-analysis, such as expert opinion. The use of informative missingness parameters in pairwise meta-analysis of aggregate data with binary outcomes has been previously implemented in Stata by the `metamiss` command. In this article, we present the new command `metamiss2`, which is an extension of `metamiss` for binary or continuous data in pairwise or network meta-analysis. The command can be used to explore the robustness of results to different assumptions about the missing data via sensitivity analysis.

Keywords: st0540, metamiss2, informative missingness, mixed treatment comparison, sensitivity analysis, meta-analysis

1 Introduction

Missing outcome data are a common threat to the validity of randomized trials and, subsequently, their meta-analysis. Because missing data are by definition not present in the dataset, addressing them requires making untestable assumptions. Researchers undertaking meta-analyses typically ignore missing data and analyze complete data only; we refer to such an analysis as an available cases analysis (ACA).

Assumptions about missing data were classified by Little and Rubin (2002). In the randomized trial setting, data are missing completely at random if the probability of a missing outcome is unrelated to any baseline variables, randomized group, or outcome. Data are missing at random (MAR) if the probability of a missing outcome is unrelated to the outcome, conditional on baseline variables and a randomized group. With no baseline variables, MAR means that missing outcomes do not differ systematically from observed outcomes in the same randomized group. An ACA therefore assumes MAR. Data are missing not at random (MNAR) if they are not MAR: that is, if the probability of a missing outcome is related to the outcome, conditional on baseline variables and a randomized group. If data are MNAR, then an ACA is likely to be biased.

Here we consider randomized trials with an outcome measured at a single time point, for which outcome data are unavailable for some of the participants within the trial. Furthermore, we focus on approaches that are based on aggregate (summary) data from the trial, such as are often available from journal articles, and that are typical of the data available for a meta-analysis.

The use of pattern mixture models has been previously suggested for handling missing outcome data in meta-analysis of binary outcomes with aggregate data (White, Higgins, and Wood 2008). This approach is based on the informative missingness odds ratio (IMOR), which relates the odds of outcome in the missing data to that in the observed data. The approach can allow for uncertainty in the IMOR and has been implemented in Stata in the `metamiss` command.

Parameters like the IMOR that measure departure from a MAR assumption have been called sensitivity parameters by Kenward, Goetghebeur, and Molenberghs (2001); we follow White, Kalaitzaki, and Thompson (2011) in calling them informative missingness parameters (IMPs). Mavridis et al. (2015) extended the IMP framework to meta-analyses with continuous outcomes by defining IMPs that relate the mean of the outcome between the missing and the observed participants.

Network meta-analysis (NMA) combines the results of multiple direct comparisons (Salanti et al. 2008) and is therefore prone to the same biases as pairwise meta-analysis. More specifically, incorrectly handling missing data in one or more comparisons of a NMA could affect all relative effects in which this particular comparison is involved either directly or indirectly (Salanti et al. 2014). Methods used to allow for IMPs in pairwise meta-analysis apply directly to NMA when only two-group trials are included. In the presence of multigroup trials, the "adjusted" covariance between relative effects from the same study also needs to be estimated (Mavridis et al. 2015). The application of

IMPs in NMA with binary outcome data has been exemplified in a Bayesian framework by Spineli et al. (2013).

The aim of this article is to introduce a new Stata command, `metamiss2`, with new syntax, which extends `metamiss` by handling continuous and binary outcome data and by working in NMA and pairwise meta-analysis. `metamiss2` performs a two-stage analysis: stage 1 estimates the "adjusted" study-specific relative effects and their variances and covariances, and stage 2 calls `metan` (Harris et al. 2008) or `metaan` (Kontopantelis and Reeves 2010) (for pairwise meta-analysis) and `network meta` (White 2015) (for NMA) to obtain the summary effects.

2 Theory

This section describes stage 1 of the analysis, which estimates the treatment effects and their variances for each study allowing for MNAR data. The second stage combines the first-stage estimates using a standard meta-analysis procedure (Palmer and Sterne 2016) and is not further described here. We describe first the case of binary data and then of continuous data. Our notation follows that of Mavridis et al. (2015) but is extended to cover the case of binary data as in White, Higgins, and Wood (2008).

2.1 Binary outcome data

We assume we have data from multiple studies, each with two groups denoted T (treatment) and C (control). We assume that in the jth group of the ith study ($j = C, T$), we know n_{ij}, the number of participants providing outcome data, and m_{ij}, the number of participants with missing outcome data. We also assume we know r_{ij}, the number of observed successes.

The model for the observed data is $r_{ij} \sim \text{Bin}(n_{ij}, \chi_{ij}^{\text{obs}})$. Then, χ_{ij}^{obs} is the "true" mean of the observed outcomes in the jth group of the ith study.

Our measure of interest in the ith study is defined as

$$\beta_i = f(\chi_{iT}^{\text{tot}}) - f(\chi_{iC}^{\text{tot}}) \tag{1}$$

where χ_{ij}^{tot} is the true mean outcome of all (observed and missing) outcomes in the jth group of the ith study. The link function $f(\cdot)$ may be the identity function $f(x) = x$ (so that the measure of interest is the risk difference), the logarithmic function $f(x) = \log(x)$ (giving the log risk-ratio), or the logit function $f(x) = \text{logit}(x)$ (giving the log odds-ratio).

In this simple setting, a MAR assumption would imply that $\chi_{ij}^{\text{tot}} = \chi_{ij}^{\text{obs}}$ (Little and Rubin 2002). Under MNAR, we view the mean outcome of all participants as a mixture of outcomes in the observed and in the missing participants. We write

$$\chi_{ij}^{\text{tot}} = \pi_{ij}\chi_{ij}^{\text{obs}} + (1 - \pi_{ij})\chi_{ij}^{\text{miss}} \tag{2}$$

where $\pi_{ij} \sim \text{Beta}(n_{ij}, m_{ij})$ is the probability of a participant being observed in the data and χ_{ij}^{miss} is the (unobserved) mean outcome in the missing data. We introduce the IMP as

$$\lambda_{ij} = g(\chi_{ij}^{\text{miss}}) - g(\chi_{ij}^{\text{obs}}) \tag{3}$$

We consider the case where g is the logit function $g(x) = \text{logit}(x)$ and the IMP is the log of IMOR (White, Higgins, and Wood 2008). When $\lambda_{ij} = 0$, we assume that the outcome in the missing participants is on average the same as the outcome in the observed participants. This is equivalent to assuming MAR. We quantify departures from the MAR assumption by allowing λ_{ij} to assume nonzero values.

2.2 Continuous outcome data

If the outcome is continuous, we assume we again know n_{ij}, m_{ij}. We also know x_{ij}^{obs}, the mean of the observed outcomes, and s_{ij}, the standard deviation (SD) of the observed outcomes.

The model for the observed data is $x_{ij}^{\text{obs}} \sim N(\chi_{ij}^{\text{obs}}, s_{ij}^2)$. The measure of interest is obtained from (1), where f may be the identity function $f(x) = x$ (giving the mean difference) or the logarithmic function $f(x) = \log(x)$ (giving the log ratio of means); alternatively, $f(x)$ may be replaced by $f_i(x) = x/\sigma_i$, where σ_i is the pooled SD in the ith study, giving the standardized mean difference (White and Thomas 2005).

The IMP (λ_{ij}) is then expressed using (2) and (3). For a continuous outcome, g may be the identity function $g(x) = x$ (so the IMP is the informative missingness difference of means or IMDOM) or the logarithmic function $g(x) = \log(x)$ (so the IMP is the log of the informative missingness ratio of means or logIMROM) (Mavridis et al. 2015). We generally expect researchers to use IMDOM with mean difference and standardized mean difference and IMROM with ratio of means.

2.3 Estimation

The IMPs λ_{ij} are required to estimate β_i but are not identified by the observed data. Instead, they are specified by the analyst on the basis of subject-matter knowledge or a range of values is assumed in a sensitivity analysis. By allowing for uncertainty in the IMPs, the model reduces the relative weight given to studies with more missing data (White, Higgins, and Wood 2008). The IMPs may be specified as independent across groups, $\lambda_{ij} \sim N(\mu_{\lambda_{ij}}, \sigma^2_{\lambda_{ij}})$, or we can allow for correlation by assuming a bivariate normal distribution with $\text{corr}(\lambda_{iT}, \lambda_{iC}) = \rho_{\lambda_i}$. Thus, nonzero values of any of $\mu_{\lambda_{iT}}$, $\mu_{\lambda_{iC}}$, $\sigma^2_{\lambda_{iT}}$, and $\sigma^2_{\lambda_{iC}}$ imply MNAR. The IMPs are assumed to be independent across studies to abide by the fundamental assumption of independent studies in meta-analysis.

Two estimation procedures are described briefly here and in more detail in Mavridis et al. (2015). We write $\beta_i = \beta_i(\theta_i)$, where $\theta_i = (\pi_{iT}, \pi_{iC}, \chi_{iT}^{\text{obs}}, \chi_{iC}^{\text{obs}}, \lambda_{iT}, \lambda_{iC})$. In the Taylor method, which uses a linear approximation to $\beta_i(\theta_i)$, the point estimate of β_i is $\widehat{\beta}_i = \beta_i(\widehat{\theta}_i)$, where $\widehat{\theta}_i = (\widehat{\pi}_{iT}, \widehat{\pi}_{iC}, \widehat{\chi}_{iT}^{\text{obs}}, \widehat{\chi}_{iC}^{\text{obs}}, \lambda_{iT}, \lambda_{iC})$, and its estimated variance is

$\widehat{\text{var}}(\widehat{\beta}_i) = D_i^T V_i D_i$, where $D_i = (d\beta_i)/(d\theta_i)$ is evaluated at $\theta_i = \widehat{\theta}_i$ and $V_i = \widehat{\text{var}}(\widehat{\theta}_i)$ is a block diagonal matrix combining the sampling variance for $\widehat{\pi}_{iT}$, $\widehat{\pi}_{iC}$, $\widehat{\chi}_{iT}^{\text{obs}}$, and $\widehat{\chi}_{iC}^{\text{obs}}$ and the uncertainty variance for $\mu_{\lambda_{iT}}$ and $\mu_{\lambda_{iC}}$. In the parametric bootstrap method, which avoids the linear approximation to $\beta_i(\theta_i)$, values θ_i^* are repeatedly drawn—π_{iT}, π_{iC}, χ_{iT}^{obs}, and χ_{iC}^{obs} independently from their posterior distributions given the data, and λ_{iT} and λ_{iC} jointly from their prior distribution—and the point estimate $\widehat{\beta}$ and its estimated variance are the mean and variance of the $\beta_i(\theta_i^*)$. When the measure of interest is the standardized mean difference, the procedure takes σ_i as the pooled SD across groups and ignores uncertainty in σ_i.

The same methods are used for multigroup studies, which may arise in NMA. Multigroup studies yield multiple treatment effects, for example, $\beta_{i1} = f(\chi_{iT1}^{\text{tot}}) - f(\chi_{iC}^{\text{tot}})$ and $\beta_{i2} = f(\chi_{iT2}^{\text{tot}}) - f(\chi_{iC}^{\text{tot}})$. Extending the estimation method above yields estimates of their variances and the covariance $\text{cov}(\widehat{\beta}_{i1}, \widehat{\beta}_{i2})$ (Mavridis et al. 2015).

3 The metamiss2 command

3.1 Syntax

`metamiss2` [*varlist*] [*if*] [*in*] [`, imptype(imdom|logimrom)`
`impmean(# #...#) impsd(# #...#) impcorrelation(`*real*|*exp*|*matrix*`)`
`compare(`*string*`) sensitivity smd md rom sdpool(on|off) rr or rd taylor`
`bootstrap reps(`*integer*`) seed(`*integer*`) fixed tau2(`*string*`) inconsistency`
`nometa metanoptions(`*meta_options*`) networkoptions(`*network_meta_options*`)`
`nokeep varchange netplot trtlabels(`*string*`)`
`netplotreference(`*string*`) netplotoptions(`*intervalplot_options*`)`]

where *varlist* is

- for pairwise meta-analysis with continuous outcome data: `nE mE yE sdE nC mC yC sdC`—variables containing the numbers of observed and missing participants and the mean and SD of the observed data in experimental and control groups, respectively.
- for pairwise meta-analysis with binary outcome data: `rE fE mE rC fC mC`—variables containing the numbers of successes and failures in the observed data and the number of missing participants in experimental and control groups, respectively.
- for NMA: *varlist* is not used, but the data must have been prepared using the `network setup` command (White 2015) in the "augmented" format (see example 4.3).

3.2 Options

Options for specifying the IMPs

`imptype(imdom | logimrom)` specifies the type of IMP for continuous outcome data. `imdom` indicates the informative missingness difference of means, and `logimrom` indicates the log of the informative missingness ratio of means. The default is `imptype(imdom)`. This option is not needed for binary outcome data because the only available IMP is logIMOR. For details on IMDOM, logIMROM, and logIMOR, see section 2, Mavridis et al. (2015), and White, Higgins, and Wood (2008).

`impmean(# #... #)` specifies the mean of the assumed (normal) distribution for IMP. The default value is 0 in all groups. If one value is given, it is the mean for all groups. For pairwise meta-analysis, if two values are given, they are the means for the experimental and control group. For NMA, if T values are given (with T the total number of treatments), they are the means for the reference treatment and the nonreference treatments in the order shown in `network setup` (White 2015). Each # may be a single value corresponding to all studies or a variable containing study-specific values.

`impsd(# #... #)` specifies the SD of the assumed (normal) distribution for IMP in the same way as described above for `impmean()`. The default value is `impsd(0)` in all groups.

`impcorrelation(`*real* | *exp* | *matrix*`)` specifies the correlation of the IMP between the different groups. The default value is `impcorrelation(0)`. A common correlation value for all pairs of treatments or the full correlation matrix (only for NMA) can be specified.

`compare(`*string*`)` specifies a second assumption for IMP to be compared with the primary analysis. *string* may include `impmean()`, `impsd()`, and `impcorrelation()`.

`sensitivity` specifies a sensitivity analysis for the IMP assuming a range of different standard deviations for its distribution with `impmean(0)` or a different specified `impmean()`.

Options for continuous data

`smd` specifies the standardized mean difference as the measure of interest (the default for continuous data).

`md` specifies the mean difference as the measure of interest.

`rom` specifies the ratio of means as the measure of interest.

`sdpool(on | off)` specifies whether the SD is pooled across groups in computing variances. Following `metan`, the default option for mean difference and ratio of means is `sdpool(off)`; for standardized mean difference, the default option is `sdpool(on)`.

Options for binary data

`rr` specifies the risk ratio (RR) as the measure of interest (the default for binary data). Note that in this case, the IMP is the logIMOR.

`or` specifies the odds ratio as the measure of interest. Note that in this case, the IMP is the logIMOR.

`rd` specifies the risk difference as the measure of interest. Note that in this case, the IMP is logIMOR.

Estimation options

`taylor` specifies that Taylor-series approximation be used to integrate over the distribution of the IMP (the default).

`bootstrap` specifies that parametric bootstrap be used to integrate over the distribution of the IMP.

`reps(`*integer*`)` specifies the number of simulations under the bootstrap method. The default is `reps(10000)`.

`seed(`*integer*`)` specifies the initial value of the random-number seed for the bootstrap method. The default is `seed(0)`. See [R] **set seed** for more details.

Meta-analysis options

`fixed` specifies the use of the fixed-effect model instead of the default random-effects model.

`tau2(`*string*`)` specifies the use of an estimator for the heterogeneity variance. This option is available only for pairwise meta-analysis, and valid estimators are the available estimators in `metaan` (Kontopantelis and Reeves 2010). The default is the DerSimonian and Laird estimator using `metan` (Harris et al. 2008).

`inconsistency` specifies the use of an inconsistency model for the case of NMA instead of the consistency model, which is the default.

`nometa` skips the conduct of pairwise or network meta-analysis after estimating the "adjusted" study-specific effect sizes and variances.

`metanoptions(`*meta_options*`)` specifies any valid options of `metan` (Harris et al. 2008).

`networkoptions(`*network_meta_options*`)` specifies any valid options of `network meta` (White 2015).

Output options

`nokeep` specifies that study-specific "adjusted" effect sizes and standard errors and variances be dropped from the dataset. By default, these estimates are stored as extra variables for pairwise meta-analysis with names `_ES`, `_seES` (as in `metan`) and in NMA with prefix `_imp_`.

`varchange` specifies that the "adjusted" study-specific relative effects and variances be stored in the dataset, replacing the respective values obtained from the `network setup` command. This means that the current assumptions about the missing data will also apply to future analyses of the data.

`netplot` specifies that a forest plot with the relative effects from NMA be drawn. The same forest plot can be produced by running the `intervalplot` command (Chaimani and Salanti 2015) after `metamiss2` for a network meta-analysis. Note that for the case of pairwise meta-analysis, a forest plot is produced by default.

`trtlabels(`*string*`)` specifies the labels of the treatments for the case of NMA. These labels, separated with spaces, will be used in the forest plot. The first label should correspond to the reference treatment, and the other treatment should be given in the numerical or alphabetical order of their codes in the data.

`netplotreference(`*string*`)` specifies a treatment to be used as a reference in the forest plot so that only a subset of the relative effects from the NMA (that is, every treatment versus that reference) will be given in the forest plot. The treatment specified here can be different from the reference treatment of the analysis.

`netplotoptions(`*intervalplot_options*`)` specifies any valid options of `intervalplot` (Chaimani and Salanti 2015).

4 Examples

4.1 Pairwise meta-analysis, binary data

We illustrate the use of `metamiss2` for meta-analysis with binary aggregate outcome data using a dataset that includes 17 trials comparing the effectiveness of haloperidol with placebo for the treatment of schizophrenia. The outcome is clinical response, and RR > 1 suggests that haloperidol works better that placebo.

```
. use http://www.mtm.uoi.gr/images/haloperidol.dta
. list, clean noobs
```

author	year	rh	fh	mh	rp	fp	mp
Arvanitis	1997	25	25	2	18	33	0
Beasley	1996	29	18	22	20	14	34
Bechelli	1983	12	17	1	2	28	1
Borison	1992	3	9	0	0	12	0
Chouinard	1993	10	11	0	3	19	0
Durost	1964	11	8	0	1	14	0
Garry	1962	7	18	1	4	21	1
Howard	1974	8	9	0	3	10	0
Marder	1994	19	45	2	14	50	2
Nishikawa_82	1982	1	9	0	0	10	0
Nishikawa_84	1984	11	23	3	0	13	0
Reschke	1974	20	9	0	2	9	0
Selman	1976	17	1	11	7	4	18
Serafetinides	1972	4	10	0	0	13	1
Simpson	1967	2	14	0	0	7	1
Spencer	1992	11	1	0	1	11	0
Vichaiya	1971	9	20	1	0	29	1

We explore different assumptions about the association of the outcome between missing and observed data, which we describe by the logIMOR.

First, we assume that our beliefs about the missing data can be expressed as follows. In the haloperidol group, we believe there may be systematic differences between outcomes in missing and observed participants, but we are not sure in which direction, so we give the logIMOR a distribution with mean 0 and SD 1. In the placebo group, we believe the response in missing participants is probably worse than in observed participants, so we give the logIMOR a distribution with mean -1 and SD 1. This can be the case, for example, when patients drop out of the study because their symptoms have worsened. We use the default method of estimation, which is Taylor-series approximation. We use the `metan` option `lcols(author)` to label the studies.

```
. metamiss2 rh fh mh rp fp mp, impmean(0 -1) impsd(1) metanopt(lcols(author))
*********************************************************************
******** METAMISS2: meta-analysis allowing for missing data *******
******** Informative missingness parameter with uncertainty *******
*********************************************************************
Informative missingness parameter: logIMOR
Measure of interest:               Risk ratio
Assumed distribution for IMP:      Experimental group ~ N(0,1^2)
                                   Control group ~ N(-1,1^2)
IMP correlation between groups:    0
Method for first stage model:      Taylor series approximation
Second stage model:                Random effects meta-analysis
(Calling metan with options: lcols(author) ...)
           Study     |     ES    [95% Conf. Interval]     % Weight
---------------------+-------------------------------------------------
Arvanitis            |  1.417       0.890     2.256         18.58
Beasley              |  1.323       0.720     2.432         14.50
Bechelli             |  6.333       1.547    25.918          4.39
Borison              |  7.000       0.400   122.442          1.19
Chouinard            |  3.492       1.113    10.955          6.21
Durost               |  8.684       1.258    59.946          2.51
Garry                |  1.791       0.596     5.381          6.60
Howard               |  2.039       0.670     6.208          6.48
Marder               |  1.381       0.758     2.517         14.72
Nishikawa_82         |  3.000       0.137    65.903          1.03
Nishikawa_84         |  9.200       0.580   146.044          1.28
Reschke              |  3.793       1.058    13.604          5.19
Selman               |  1.949       0.906     4.194         11.09
Serafetinides        |  8.764       0.516   148.917          1.22
Simpson              |  2.526       0.135    47.152          1.14
Spencer              | 11.000       1.671    72.396          2.62
Vichaiya             | 19.393       1.180   318.749          1.25
---------------------+-------------------------------------------------
D+L pooled ES        |  2.211       1.607     3.042        100.00
---------------------+-------------------------------------------------
  Heterogeneity chi-squared =  20.66 (d.f. = 16) p = 0.192
  I-squared (variation in ES attributable to heterogeneity) =  22.6%
  Estimate of between-study variance Tau-squared =  0.0863
  Test of ES=1 : z=   4.87 p = 0.000
```

After we run `metamiss2`, the "adjusted" study-specific relative effects along with their 95% confidence intervals are given in the output. The same results are obtained when we run the same analysis with `metamiss`:

```
. metamiss rh fh mh rp fp mp, logimor(0 -1) sdlogimor(1) method(Taylor)
> randomi lcols(author)
***********************************************************************
******** METAMISS: meta-analysis allowing for missing data ********
********           Bayesian analysis using priors          ********
***********************************************************************
Measure: RR.
Zero cells detected: adding 1/2 to 6 studies.
Priors used:  Group 1: N(0,1^2). Group 2: N(-1,1^2). Correlation: 0.
Method: Taylor series approximation.
(Calling metan with options:  randomi lcols(author) eform  ...)
          Study     |     ES    [95% Conf. Interval]     % Weight
--------------------+-------------------------------------------------
Arvanitis           |  1.417       0.890     2.256         18.58
Beasley             |  1.323       0.720     2.432         14.50
Bechelli            |  6.333       1.547    25.918          4.39
Borison             |  7.000       0.400   122.442          1.19
Chouinard           |  3.492       1.113    10.955          6.21
Durost              |  8.684       1.258    59.946          2.51
Garry               |  1.791       0.596     5.381          6.60
Howard              |  2.039       0.670     6.208          6.48
Marder              |  1.381       0.758     2.517         14.72
Nishikawa_82        |  3.000       0.137    65.903          1.03
Nishikawa_84        |  9.200       0.580   146.044          1.28
Reschke             |  3.793       1.058    13.604          5.19
Selman              |  1.949       0.906     4.194         11.09
Serafetinides       |  8.764       0.516   148.917          1.22
Simpson             |  2.526       0.135    47.152          1.14
Spencer             | 11.000       1.671    72.396          2.62
Vichaiya            | 19.393       1.180   318.749          1.25
--------------------+-------------------------------------------------
D+L pooled ES       |  2.211       1.607     3.042        100.00
--------------------+-------------------------------------------------
  Heterogeneity chi-squared =  20.66 (d.f. = 16) p = 0.192
  I-squared (variation in ES attributable to heterogeneity) =  22.6%
  Estimate of between-study variance Tau-squared =  0.0863
  Test of ES=1 : z=   4.87 p = 0.000
```

The above analysis implicitly assumes that the IMPs in the two groups are unrelated. We next assume that a high logIMOR in one group is likely to go with a high logIMOR in the other group; that entails the two logIMORs are positively correlated, with correlation $\rho = 0.5$. We obtain the study-specific RRs using the bootstrap method:

```
. metamiss2 rh fh mh rp fp mp, impmean(0 -1) impsd(1) impc(0.5) bootstrap
> metanopt(lcols(author))

*****************************************************************
******** METAMISS2: meta-analysis allowing for missing data *******
******** Informative missingness parameter with uncertainty *******
*****************************************************************

Informative missingness parameter: logIMOR
Measure of interest:               Risk ratio
Assumed distribution for IMP:      Experimental group ~ N(0,1^2)
                                   Control group ~ N(-1,1^2)
IMP correlation between groups:    .5
Method for first stage model:      Parametric Bootstrap (10000 draws)
Second stage model:                Random effects meta-analysis

(Calling metan with options: lcols(author) ...)

           Study     |     ES    [95% Conf. Interval]     % Weight
---------------------+-------------------------------------------------
Arvanitis            |  1.430       0.893     2.290         17.87
Beasley              |  1.305       0.762     2.238         16.43
Bechelli             |  7.878       1.582    39.235          4.45
Borison              | 21.496       0.275  1682.770          0.71
Chouinard            |  3.951       1.125    13.880          6.53
Durost               | 14.575       1.235   172.078          2.10
Garry                |  1.882       0.581     6.093          7.20
Howard               |  2.249       0.672     7.529          6.91
Marder               |  1.393       0.758     2.559         15.03
Nishikawa_82         |  7.315       0.068   787.967          0.62
Nishikawa_84         | 31.262       0.443  2205.611          0.75
Reschke              |  4.710       1.075    20.641          5.09
Selman               |  1.990       0.925     4.284         12.17
Serafetinides        | 27.359       0.308  2427.858          0.67
Simpson              |  6.899       0.078   612.395          0.67
Spencer              | 18.644       1.565   222.118          2.08
Vichaiya             | 64.289       0.820  5040.384          0.71
---------------------+-------------------------------------------------
D+L pooled ES        |  2.329       1.603     3.384        100.00
---------------------+-------------------------------------------------

  Heterogeneity chi-squared =  23.32 (d.f. = 16) p = 0.105
  I-squared (variation in ES attributable to heterogeneity) =  31.4%
  Estimate of between-study variance Tau-squared =  0.1455

  Test of ES=1 : z=   4.44 p = 0.000
```

Running the same analysis with `metamiss` gives slightly different results:

```
. metamiss rh fh mh rp fp mp, logimor(0 -1) sdlogimor(1) corrlogimor(0.5)
 method(mc)randomi lcols(author) reps(10000)
*****************************************************************
******** METAMISS: meta-analysis allowing for missing data ********
********           Bayesian analysis using priors          ********
*****************************************************************
Measure: logRR.
Zero cells detected: adding 1/2 to 6 studies.
Priors used:  Group 1: N(0,1^2). Group 2: N(-1,1^2). Correlation: 0.5.
Method: Monte Carlo (10000 draws).
.....................................................................
> .....................................................................
> .....................................................................
> .....................................................................
  (output omitted)
(Calling metan with options:  randomi lcols(author) eform  ...)
           Study     |     ES    [95% Conf. Interval]     % Weight
---------------------+-------------------------------------------------
Arvanitis            |  1.410       0.890     2.233         17.24
Beasley              |  1.297       0.761     2.210         14.92
Bechelli             |  5.283       1.506    18.533          4.39
Borison              |  4.024       0.537    30.136          1.87
Chouinard            |  3.195       1.101     9.274          5.78
Durost               |  6.289       1.350    29.296          3.07
Garry                |  1.745       0.616     4.942          6.01
Howard               |  1.966       0.693     5.575          5.99
Marder               |  1.372       0.760     2.476         13.33
Nishikawa_82         |  2.042       0.222    18.802          1.55
Nishikawa_84         |  5.173       0.774    34.552          2.08
Reschke              |  3.472       1.122    10.749          5.25
Selman               |  1.948       0.915     4.149          9.73
Serafetinides        |  4.875       0.666    35.680          1.91
Simpson              |  1.639       0.206    13.040          1.76
Spencer              |  7.859       1.719    35.943          3.13
Vichaiya             |  9.862       1.414    68.796          2.00
---------------------+-------------------------------------------------
D+L pooled ES        |  2.141       1.613     2.843        100.00
---------------------+-------------------------------------------------

  Heterogeneity chi-squared =  20.27 (d.f. = 16) p = 0.208
  I-squared (variation in ES attributable to heterogeneity) =  21.1%
  Estimate of between-study variance Tau-squared =  0.0663

  Test of ES=1 : z=   5.26 p = 0.000
```

This difference in results is due to a) random error of the simulations and b) the different way the two commands handle studies without missing participants in one or both groups. More specifically, for these trials, `metamiss2` assumes that the probability of observing the data is $\pi_{ij} = 1$, while `metamiss` assumes that the probability is not constant but a random variable.

An important advantage of `metamiss2` when using the bootstrap method is that it runs much faster (that is, about 10 times) than `metamiss` because of coding in Mata.

4.2 Pairwise meta-analysis, continuous data

The second example involves data from eight trials that compare the effectiveness of mirtazapine versus placebo for major depression. The outcome is change in depression symptoms measured on a standardized rating scale [Hamilton Depression Rating Scale 21-Item (HAMD 21) depression scale].

```
. use http://www.mtm.uoi.gr/images/mirtazapine.dta, clear
. list, clean noobs
```

id	study	yp	sdp	np	mp	ym	sdm	nm	mm
1	Claghorn1995	-11.4	10.2	19	26	-14.5	8.8	26	19
2	MIR 003-003	-11.5	8.3	24	21	-14	7.3	27	18
3	MIR 003-008	-11.4	8	17	13	-13.2	8	12	18
4	MIR 003-020	-6.2	6.5	24	19	-13	9	23	21
5	MIR 003-021	-17.4	5.3	21	29	-13.8	5.9	22	28
6	MIR 003-024	-11.1	9.9	27	23	-15.7	6.7	30	20
7	MIR 84023a	-11.9	8.6	33	24	-14.2	7.6	35	25
8	MIR 84023b	-11.8	8.3	48	18	-14.7	8.4	51	13

We first describe the departure from MAR using the IMDOM. We assume a systematic departure from the MAR assumption where for the mirtazapine group, IMDOM has mean -0.5 with SD(IMDOM) $= 1$ and where for the placebo group, IMDOM has mean 1 with SD(IMDOM) $= 1.5$. This means that we think it is likely that missing participants had better outcomes than observed participants in the mirtazapine group (for example, they left the study because of early response with important side effects), while the opposite is true in the placebo group (for example, they left the study because of lack of efficacy). We also assume that IMDOMs are correlated between the two groups with $\rho = 0.5$, and we compare the results with ACA (that is, when IMP $= 0$ without uncertainty):

```
. metamiss2 nm mm ym sdm np mp yp sdp, impmean(-0.5 1) impsd(1 1.5) impcorr(0.5)
> compare(impmean(0) impsd(0)) md metanopt(lcols(study))

Primary analysis

**********************************************************************
******** METAMISS2: meta-analysis allowing for missing data *******
******** Informative missingness parameter with uncertainty *******
**********************************************************************

Informative missingness parameter: IMDOM
Measure of interest:               Mean difference
Assumed distribution for IMP:      Experimental group ~ N(-.5,1^2)
                                   Control group ~ N(1,1.5^2)
IMP correlation between groups:    .5
Method for first stage model:      Taylor series approximation
Second stage model:                Random effects meta-analysis

(Calling metan with options: lcols(study) ...)

Secondary analysis

**********************************************************************
******** METAMISS2: meta-analysis allowing for missing data *******
********               Available cases analysis            ********
**********************************************************************

Informative missingness parameter: IMDOM
Measure of interest:               Mean difference
Method for first stage model:      Taylor series approximation
Second stage model:                Random effects meta-analysis

(Calling metan with options: lcols(study) ...)

           Study     |     ES    [95% Conf. Interval]
---------------------+-------------------------------------------------
     Primary analysis
Claghorn1995         |   -3.889    -9.783     2.005
MIR 003-003          |   -3.167    -7.653     1.319
MIR 003-008          |   -2.533    -8.583     3.516
MIR 003-020          |   -7.480   -12.143    -2.818
MIR 003-021          |    2.740    -0.940     6.420
MIR 003-024          |   -5.260    -9.860    -0.660
MIR 84023a           |   -2.929    -6.956     1.097
MIR 84023b           |   -3.274    -6.645     0.096
 Sub-total           |
  D+L pooled ES      |   -3.046    -5.264    -0.828
---------------------+-------------------------------------------------
     Secondary analysis
Claghorn1995         |   -3.100    -8.799     2.599
MIR 003-003          |   -2.500    -6.814     1.814
MIR 003-008          |   -1.800    -7.712     4.112
MIR 003-020          |   -6.800   -11.305    -2.295
MIR 003-021          |    3.600     0.251     6.949
MIR 003-024          |   -4.600    -9.038    -0.162
MIR 84023a           |   -2.300    -6.166     1.566
MIR 84023b           |   -2.900    -6.191     0.391
 Sub-total           |
  D+L pooled ES      |   -2.382    -4.729    -0.035
---------------------+-------------------------------------------------
```

```
Test(s) of heterogeneity:
               Heterogeneity  degrees of
                 statistic     freedom      P    I-squared**   Tau-squared
Primary analysis    13.92          7      0.053     49.7%       4.9682
Secondary analysis  16.92          7      0.018     58.6%       6.5355
** I-squared: the variation in ES attributable to heterogeneity)

Significance test(s) of ES=0
Primary analysis      z=  2.69     p = 0.007
Secondary analysis    z=  1.99     p = 0.047
------------------------------------------------------------------------------
```

Next, we change the IMP to the IMROM. To investigate how the summary effect and its variance changes under different levels of uncertainty assumed for the IMP, we run a sensitivity analysis with IMROM = 1 on a range of different values for SD(*log*IMROM) using the bootstrap method:

```
. metamiss2 nm mm ym sdm np mp yp sdp, md sensitivity imptype(logimrom)
******************************************************************
******** METAMISS2: meta-analysis allowing for missing data *******
******** Informative missingness parameter with uncertainty *******
****    Sensitivity analysis assuming departures from MAR     *****
******************************************************************
```

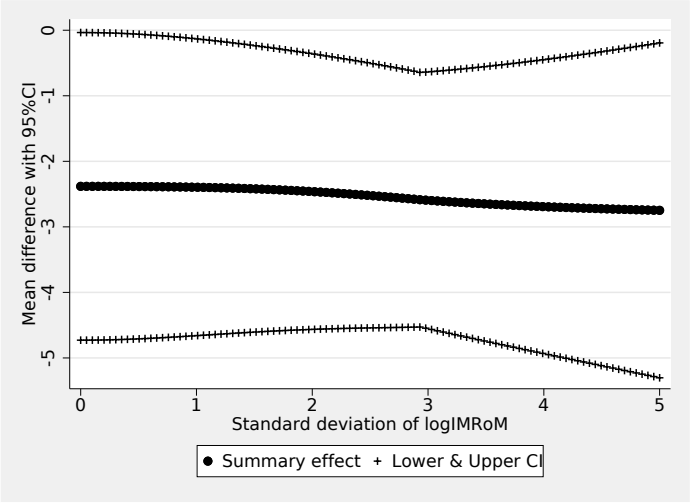

Figure 1. Plot of the summary mean difference of mirtazapine versus placebo and the respective 95% confidence interval (random-effects meta-analysis) for various values of SD(*log*IMROM) under the IMROM = 1 assumption

Figure 1 shows that increasing the uncertainty of the IMP results in a narrower confidence interval for the summary effect up to some point ($\sim$ SD = 3); this is related to the reduction of heterogeneity due to the extra variance introduced in the study-

specific estimates. However, when large uncertainty is assumed for IMP (SD $>$ 3), then this uncertainty is also reflected in the summary effect; therefore, the confidence interval becomes wider.

4.3 Network meta-analysis

To illustrate the use of `metamiss2` in NMA, we use a dataset that comprises a network of 12 trials comparing the effectiveness of 9 antidepressants. The outcome is again measured as the change score on the Hamilton Depression Rating Scale 21-Item (HAMD 21) depression scale.

```
. use http://www.mtm.uoi.gr/images/antidepressants.dta, clear
. list, clean noobs
```

id	t	y	sd	n	m
1	1	9	8.65	41	8
2	1	7.56	12.31	39	1
3	2	17.2	11.1	74	23
4	2	13.5	2.1	12	15
5	3	6.55	5.23	20	5
6	4	7	5	45	0
7	4	9.6	6.2	63	19
8	5	10.4	9.12	37	163
9	5	15.8	3.3	30	3
10	6	8.2	7.52	55	20
11	7	7.4	7.52	16	2
12	6	12	8.65	89	32
1	8	4.6	8.65	39	13
2	4	11.27	11.33	45	3
3	6	14.2	11.1	75	18
4	4	13.8	1.8	15	11
5	4	7.76	2.89	21	3
6	9	6	5	43	1
7	9	8.4	5.4	67	11
8	4	11	9.12	55	145
9	6	18.7	5.1	32	2
10	9	8.7	7.52	55	15
11	6	10.4	7.52	15	3
12	9	11.3	8.65	91	37

Because of the complicated structure of data, `metamiss2` does not take arguments for the outcome when applied to NMA. Instead, the command `metamiss2` will be executed after the data have been set up with the `network setup` command (White 2015). This applies to any type of outcome that is handled with the `network setup` command.

We first prepare the data in the "augmented" format using the `network` package (version 1.2.3 here) that calls `mvmeta` (version 3.1.3 here):

```
. network setup y sd n, trt(t) stud(id) nmiss(m) nocodes
Treatments used
   1 (reference):                      1
   2:                                  2
   3:                                  3
   4:                                  4
   5:                                  5
   6:                                  6
   7:                                  7
   8:                                  8
   9:                                  9
Measure                                Mean difference
   Standard deviation pooling:         off
Studies
   ID variable:                        id
   Number used:                        12
   IDs with augmented reference arm:   3 4 5 6 7 8 9 10 11 12
   - observations added:               0.00001
   - mean in augmented observations:   study-specific mean
   - SD in augmented observations:     study-specific within-arms SD
Network information
   Components:                         1 (connected)
   D.f. for inconsistency:             2
   D.f. for heterogeneity:             2
Current data
   Data format:                        augmented
   Design variable:                    _design
   Estimate variables:                 _y*
   Variance variables:                 _S*
   Command to list the data:           list id _y* _S*, noo sepby(_design)
```

We then run `metamiss2` without arguments to obtain the ACA:

```
. metamiss2
**********************************************************************
**** METAMISS2: network meta-analysis allowing for missing data ***
********               Available cases analysis            ********
**********************************************************************
Informative missingness parameter: IMDOM
Measure of interest:               Mean difference
Method for first stage model:      Taylor series approximation
Second stage model:                Random effects network meta-analysis
(Calling network meta  ...)
Command is: mvmeta _y _S  , bscovariance(exch 0.5) longparm suppress(uv mm)
> vars(_y_2 _y_3 _y_4 _y_5 _y_6 _y_7 _y_8 _y_9)
Note: using method reml
Note: using variables _y_2 _y_3 _y_4 _y_5 _y_6 _y_7 _y_8 _y_9
Note: 12 observations on 8 variables
Note: variance-covariance matrix is proportional to .5*I(8)+.5*J(8,8,1)
initial:       log likelihood = -93.187608
rescale:       log likelihood = -93.187608
rescale eq:    log likelihood = -92.973311
Iteration 0:   log likelihood = -92.973311  (not concave)
```

```
Iteration 1:   log likelihood = -92.868401  (not concave)
Iteration 2:   log likelihood = -92.865231
Iteration 3:   log likelihood = -92.863018
Iteration 4:   log likelihood = -92.863013
Multivariate meta-analysis
Variance-covariance matrix = proportional .5*I(8)+.5*J(8,8,1)
Method = reml                                 Number of dimensions    =     8
Restricted log likelihood = -92.863013        Number of observations  =    12
```

		Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
_y_2							
	_cons	3.770247	2.693254	1.40	0.162	-1.508434	9.048927
_y_3							
	_cons	2.499887	2.916042	0.86	0.391	-3.215451	8.215225
_y_4							
	_cons	3.709888	2.595755	1.43	0.153	-1.377698	8.797474
_y_5							
	_cons	.6746296	2.853338	0.24	0.813	-4.91781	6.267069
_y_6							
	_cons	2.813138	2.759187	1.02	0.308	-2.594769	8.221045
_y_7							
	_cons	-.1868627	3.862321	-0.05	0.961	-7.756873	7.383148
_y_8							
	_cons	-4.4	1.934803	-2.27	0.023	-8.192145	-.607855
_y_9							
	_cons	2.622049	2.683481	0.98	0.329	-2.637476	7.881575

```
Estimated between-studies SDs and correlation matrix:
             SD       _y_2       _y_3       _y_4       _y_5       _y_6       _y_7
_y_2  8.197e-06          1          .          .          .          .          .
_y_3  8.197e-06         .5          1          .          .          .          .
_y_4  8.197e-06         .5         .5          1          .          .          .
_y_5  8.197e-06         .5         .5         .5          1          .          .
_y_6  8.197e-06         .5         .5         .5         .5          1          .
_y_7  8.197e-06         .5         .5         .5         .5         .5          1
_y_8  8.197e-06         .5         .5         .5         .5         .5         .5
_y_9  8.197e-06         .5         .5         .5         .5         .5         .5

          _y_8       _y_9
_y_2          .          .
_y_3          .          .
_y_4          .          .
_y_5          .          .
_y_6          .          .
_y_7          .          .
_y_8          1          .
_y_9         .5          1
mvmeta command stored as F9
```

To explore the impact of alternative assumptions, we incorporate IMPs in our analysis. As in pairwise meta-analysis, IMPs can be treatment specific. There are 9 treatments in the network, and assumptions for the outcome among missing participants can be different depending on the administered treatment. Here we consider that treatments 1, 2, 6, and 8 are associated with IMDOM $= 1$; for treatments 3, 4, and 9, IMDOM $= -1$; and for treatments 5 and 7, IMDOM $= 0$. We assume SD(IMDOM) $= 1$ for all treatments in the network. Additionally, drug-specific IMDOMs can be correlated depending on the nature of missing data. Information about the pairwise correlation between the 9 IMDOMs has to be collected in a matrix. In the matrix shown below, the correlation between the IMDOMs for treatments 4 and 6 is $\rho_{4,6} = 0.5$ and between treatments 5 and 6 is $\rho_{5,6} = 0.2$:

$$C = \begin{pmatrix} 1 & 0.5 & 0.5 & 0.5 & 0.5 & 0.5 & 0.5 & 0.5 & 0.5 \\ 0.5 & 1 & 0.5 & 0.5 & 0.5 & 0.5 & 0.5 & 0.5 & 0.5 \\ 0.5 & 0.5 & 1 & 0.5 & 0.5 & 0.5 & 0.5 & 0.5 & 0.5 \\ 0.5 & 0.5 & 0.5 & 1 & 0.2 & 0.5 & 0.5 & 0.5 & 0.5 \\ 0.5 & 0.5 & 0.5 & 0.2 & 1 & 0.2 & 0.5 & 0.5 & 0.5 \\ 0.5 & 0.5 & 0.5 & 0.5 & 0.2 & 1 & 0.2 & 0.5 & 0.5 \\ 0.5 & 0.5 & 0.5 & 0.5 & 0.5 & 0.2 & 1 & 0.2 & 0.5 \\ 0.5 & 0.5 & 0.5 & 0.5 & 0.5 & 0.5 & 0.2 & 1 & 0.2 \\ 0.5 & 0.5 & 0.5 & 0.5 & 0.5 & 0.5 & 0.5 & 0.2 & 1 \end{pmatrix}$$

Note that here the choice of the correlation matrix is arbitrary, but in practice, it should be defined on the basis of expert opinion.

The matrix can be specified using the `matrix` command:

```
. matrix C=J(9,9,0.5)+0.5*I(9)
. forvalues i=4/8{
  2.         matrix C[`i´,`=`i´+1´]=0.2
  3.         matrix C[`=`i´+1´,`i´]=0.2
  4. }
. matrix list C
symmetric C[9,9]
    c1  c2  c3  c4  c5  c6  c7  c8  c9
r1   1
r2  .5   1
r3  .5  .5   1
r4  .5  .5  .5   1
r5  .5  .5  .5  .2   1
r6  .5  .5  .5  .5  .2   1
r7  .5  .5  .5  .5  .5  .2   1
r8  .5  .5  .5  .5  .5  .5  .2   1
r9  .5  .5  .5  .5  .5  .5  .5  .2   1
```

To run the analysis, the `metamiss2` command needs three arguments: the vector of the IMDOMs, the vector of their variances, and the matrix of correlations. We run the analysis using the bootstrap method:

```
. metamiss2, impmean(1 1 -1 -1 0 1 0 1 -1) impsd(1) impcorr(C) bootstrap
**********************************************************************
**** METAMISS2: network meta-analysis allowing for missing data ***
******** Informative missingness parameter with uncertainty *******
**********************************************************************
Informative missingness parameter: IMDOM
Measure of interest:               Mean difference
Assumed distribution for IMP:      1 ~ N(1,1^2)  (Reference group)
                                   2 ~ N(1,1^2)
                                   3 ~ N(-1,1^2)
                                   4 ~ N(-1,1^2)
                                   5 ~ N(0,1^2)
                                   6 ~ N(1,1^2)
                                   7 ~ N(0,1^2)
                                   8 ~ N(1,1^2)
                                   9 ~ N(-1,1^2)
IMP correlation between groups:    Matrix C
Method for first stage model:      Parametric Bootstrap (10000 draws)
Second stage model:                Random effects network meta-analysis
(Calling network meta  ...)
Command is: mvmeta _y _S  , bscovariance(exch 0.5) longparm suppress(uv mm)
> vars(_y_2 _y_3 _y_4 _y_5 _y_6 _y_7 _y_8 _y_9)
Note: using method reml
Note: using variables _y_2 _y_3 _y_4 _y_5 _y_6 _y_7 _y_8 _y_9
Note: 12 observations on 8 variables
Note: variance-covariance matrix is proportional to .5*I(8)+.5*J(8,8,1)
initial:       log likelihood = -93.083888
rescale:       log likelihood = -93.083888
rescale eq:    log likelihood = -92.739094
Iteration 0:   log likelihood = -92.739094
Iteration 1:   log likelihood = -92.674229
Iteration 2:   log likelihood = -92.672701
Iteration 3:   log likelihood = -92.672697
```

```
Multivariate meta-analysis
Variance-covariance matrix = proportional .5*I(8)+.5*J(8,8,1)
Method = reml                                  Number of dimensions    =     8
Restricted log likelihood = -92.672697         Number of observations  =    12
```

		Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
_y_2							
	_cons	4.755919	2.727856	1.74	0.081	-.5905793	10.10242
_y_3							
	_cons	2.358211	2.918266	0.81	0.419	-3.361486	8.077908
_y_4							
	_cons	3.639063	2.589696	1.41	0.160	-1.436648	8.714774
_y_5							
	_cons	1.094613	2.867561	0.38	0.703	-4.525702	6.714929
_y_6							
	_cons	3.373884	2.762537	1.22	0.222	-2.040589	8.788356
_y_7							
	_cons	.1929548	3.853219	0.05	0.960	-7.359216	7.745126
_y_8							
	_cons	-4.343083	1.933772	-2.25	0.025	-8.133206	-.5529604
_y_9							
	_cons	2.62097	2.680077	0.98	0.328	-2.631884	7.873825

```
Estimated between-studies SDs and correlation matrix:
             SD       _y_2       _y_3       _y_4       _y_5       _y_6       _y_7
_y_2  5.018e-06          1          .          .          .          .          .
_y_3  5.018e-06         .5          1          .          .          .          .
_y_4  5.018e-06         .5         .5          1          .          .          .
_y_5  5.018e-06         .5         .5         .5          1          .          .
_y_6  5.018e-06         .5         .5         .5         .5          1          .
_y_7  5.018e-06         .5         .5         .5         .5         .5          1
_y_8  5.018e-06         .5         .5         .5         .5         .5         .5
_y_9  5.018e-06         .5         .5         .5         .5         .5         .5

            _y_8       _y_9
_y_2           .          .
_y_3           .          .
_y_4           .          .
_y_5           .          .
_y_6           .          .
_y_7           .          .
_y_8           1          .
_y_9          .5          1
mvmeta command stored as F9
```

Accounting for missing outcome data in this particular example had little impact on the results, which might be due to the arbitrary assumptions we made about the IMPs. Treatment 8 appears to be more effective than treatment 1, as in the ACA. The confidence intervals of all relative effects are slightly narrower compared with ACA, while heterogeneity was estimated to be near zero.

5 Discussion

`metamiss2` and `metamiss` are almost equivalent for meta-analyses with binary outcome data, and they give identical answers when the Taylor-series method is used to account for uncertainty. However, small discrepancies exist between the two commands. First, `metamiss` has the option to perform analyses of missing binary data based on reasons for missingness (White and Higgins 2009). This approach allows different assumptions to be made within each study group at the patient level and not only on average as `metamiss2` (Higgins, White, and Wood 2008). Second, the option to use the Gauss–Hermite quadrature estimation method is not available in `metamiss2`. However, the parametric bootstrap method in `metamiss2` is very fast and thus can be used routinely as an alternative to quadrature. Note that the Monte Carlo method, which is available in `metamiss`, is fully Bayesian and thus can show small numerical differences from the parametric bootstrap method in `metamiss2`.

A limitation of `metamiss2` is that finite-sample correction for standardized mean difference has not been incorporated in the present code; this correction allows for uncertainty in the observed study-specific standard deviations when trial sample sizes are small. Future work will explore the potential to enable an assumption that IMPs are correlated across different studies (White et al. 2008, 2).

There is no unique best approach to handle missing outcome data in meta-analysis with aggregate data. ACA is usually a sensible starting point and will often be the primary analysis. Because the IMP parameters cannot be estimated from the observed data, values must be given to them based on judgment and on evidence external to the meta-analysis. Thus, sensitivity analyses using different plausible values of IMPs are necessary to assess the robustness of results to different assumptions about the missing data. The sensitivity option in `metamiss2` sets the IMP means and correlation to zero and gradually increases the IMP standard deviations. This reflects a minor departure from MAR. In practice, we would expect the IMP mean to be nonzero. We may conduct additional sensitivity analyses changing the value of both mean and SD (one at a time) of IMP parameters and assuming each of them common and different across groups and monitor how sensitive results are to these changes. Other sensitivity analysis strategies were suggested by White, Higgins, and Wood (2008). In all cases, discussion with subject matter experts is needed to choose sensible distributions for the IMPs.

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